Serum Lp(a) lipoprotein concentration is not associated with clinical and angiographic outcome five years after coronary artery bypass graft surgery

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Abstract

***Objective*—To examine the association between serum Lp(a) lipoprotein concentration and clinical and angiographic outcomes five years after coronary artery bypass graft (CABG) surgery.**

***Setting*—A regional cardiothoracic centre, Freeman Hospital, and the University Clinical Investigation Unit, Royal Victoria Infirmary, Newcastle upon Tyne.**

***Patients and design*—353 consecutive patients (56 female, 297 male, mean age 57·2 years) undergoing first time CABG surgery for stable angina were studied prospectively.**

***Main outcome measures*—Late cardiac death (beyond 30 days) and non-fatal myocardial infarction; prevalence of angina five years after surgery in 291 (94%) survivors and vein graft patency (evaluated by patient) in 118 survivors five years after surgery. Serum Lp(a) concentration and lipid profiles were measured before operation, and 3, 6, 12, and 60 months after surgery. Lipid profiles were also measured 24 months after surgery.**

***Results*—Weighted Lp(a) concentration (by tertile) was not associated with late cardiac death or with the combination of late cardiac death and non-fatal myocardial infarction, with the presence of angina, or with vein graft occlusion. The association remained non-significant if analysis was restricted to the upper tertile of LDL cholesterol (> 4·1 mmol/l) or to patients under the age of 55 years at the time of surgery.**

***Conclusions*—Serum Lp(a) concentration did not predict late cardiac death, the combination of late cardiac death and non-fatal myocardial infarction, or the prevalence of angina or vein graft occlusion five years after CABG surgery.**

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Keywords: Lp(a) lipoprotein; coronary artery bypass graft surgery; graft occlusion; angina; mortality

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Lp(a) lipoprotein was discovered in human serum more than 30 years ago.[1] Its concentration is higher in white patients with coronary artery disease than in asymptomatic members of the same population, an association which is independent of other lipid risk factors.[1] Lp(a) is made up of a low density lipoprotein particle, the apo B100 component of which is linked by a disulphide bond to a unique glycoprotein, apolipoprotein (a), which structurally is homologous to plasminogen. It is this structure that has led to the hypothesis that Lp(a) may play an important role in promoting both coronary atherosclerosis and thrombosis.

Following coronary artery bypass graft (CABG) surgery, coronary events may occur as a result of graft failure. Vein graft stenosis has been associated with high Lp(a) levels,[2] but vein graft occlusion one year after CABG surgery was not associated with high serum Lp(a) concentration.[3] Early after surgery, graft occlusion is generally a thrombotic event,[4] while atherosclerosis becomes increasingly important beyond the first year.[5] Thus, with a possible role in both thrombosis and atherosclerosis, the association between Lp(a) concentration and late outcome after CABG surgery deserves further evaluation. We report the association between Lp(a) concentration and cardiac events and vein graft occlusion in a prospective study of a consecutive group of patients undergoing CABG surgery at a single surgical centre.

Methods

SUBJECTS

During the period 25 October 1988 to 4 December 1989, 367 consecutive patients were admitted for elective first time CABG surgery to the Freeman Hospital. CABG surgery was performed for chronic stable angina or after unstable angina had settled. Fourteen patients were excluded. Eight lived outside the former Northern region, three had simultaneous valve surgery performed, and three refused to participate. Thus 353 patients (56 female, 297 male) consented and were recruited to this prospective study. The protocol for the study to five years was approved by the Newcastle joint ethics committee.

CLINICAL FOLLOW UP

Five years after CABG surgery, mortality status was established for all patients. The date and cause of death were obtained from hospital notes, copies of death certificates, necropsy mortem reports, and general practitioners. A sudden death was defined as a death occurring

without previous symptoms or within one hour of the onset of new cardiac symptoms.[6] An unwitnessed death was included in this group if the patient had been free of new symptoms for up to 24 hours before being found dead.

Forty one patients had died and three had undergone further cardiac surgery. Five years after surgery 309 patients were alive without further cardiac surgery; 253 (82%) of these patients were seen in a study clinic, four were seen at home, and 34 completed postal questionnaires. Patients were asked to report hospital admissions. General practitioners were contacted in the event of patients (n = 18) failing to respond to questionnaires. The diagnosis during any hospital admission was corroborated from hospital notes. Confirmation of events suffered while patients were abroad was through their general practitioners if possible.

Patients were asked about symptoms of angina. These were either typical symptoms or, if atypical, were the same as those experienced preoperatively. The severity of angina was classified using the Canadian Cardiovascular Society functional classification.[7]

ANGIOGRAPHIC FOLLOW UP

Coronary and graft angiography as part of the research protocol was considered after detailed clinical evaluation of patients who had not undergone repeat cardiac surgery. Patients over the age of 70 years and those thought to have a higher than usual risk of complications were excluded from these research directed angiograms. During the first 122 angiograms a higher than expected complication rate occurred and led to this part of the study being terminated prematurely.

Coronary and graft angiograms were performed using the Judkins technique and a standard protocol used to define occlusion of vein graft distal anastomosis. Native coronary arteries and grafts were visualised by selective injection of contrast. A distal vein graft anastomosis was defined as occluded if no contrast was seen to enter the recipient artery during selective injection, or alternatively by the absence of any graft opacification during aortography, preferably supplemented by evidence of either a non-occluded native artery or collaterals to that coronary artery territory.

LIPOPROTEIN (A) AND LIPID ASSAYS

Patients were studied immediately before CABG surgery, and 3, 6, 12, and 60 months after surgery. Lipid assays were also performed at 24 months. Blood samples were obtained after a 12 hour overnight fast. Total cholesterol and triglyceride concentrations were determined from serum samples and high density lipoprotein (HDL) cholesterol concentration was measured in EDTA/plasma. Lp(a) concentration was determined from stored serum samples. Previous studies confirm the reliability of Lp(a) assay in stored samples.[8]

Lp(a) was measured by an enzyme linked immunosorbent assay (ELISA; Biopool (Umea, Sweden), interassay coefficient of variation 3% to 8%), as previously described.[8] Standard enzymatic methods (Cobas Bio centrifugal analyser, Roche Products, Welwyn Garden City, UK) were used to measure serum cholesterol (cholesterol oxidase, interassay coefficient of variation 1·3% to 2·1%) and triglycerides (lipase-glycerol kinase; interassay coefficient of variation 2·7% to 9·4%). HDL cholesterol was measured after precipitation of apolipoprotein B containing lipoproteins with heparin and manganese or with phosphotungstate and magnesium, and assayed by the cholesterol oxidase method (interassay coefficient of variation 8·8% to 14·6%). Values obtained using the phosphotungstate and magnesium method were adjusted to be equivalent to those using the heparin and manganese method using the regression equation, phosphotungstate and magnesium method = 0·99 × heparin and manganese method − 0·07. Low density lipoprotein (LDL) cholesterol concentration was calculated from the Friedewald equation.[9]

STATISTICS

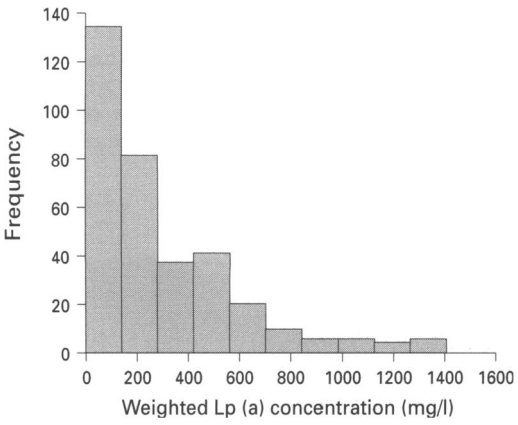
Data manipulation and analyses was performed using two statistical packages, Statview (Abacus Concepts, Inc, Berkeley, California, USA) and STATA 3·1 (STATA Corporation, College Station, Texas, USA).

Categorical variables were expressed as the number (percentage) and continuous variables as the mean (SD).

Serum Lp(a) and LDL cholesterol concentrations were measured at intervals after CABG surgery. A weighted mean was calculated for each variable. For example, weighted mean Lp(a) = [(3 × (a + b)/2) + (3 × (b + c)/2) + (6 × (c + d)/2) + (48 × (d + e)/2)]/60, where a, b, c, d, and e are the Lp(a) concentration before surgery and 3, 6, 12, and 60 months after surgery.

If patients died, weighted Lp(a) concentration was calculated for the duration of time until death. If patients alive after five years had missing measurements, the weighted mean was calculated from those measurements available for that time period.

Weighted mean Lp(a) concentration had a highly skewed distribution (figure) and was categorised into tertiles.



Distribution of weighted serum Lp(a) concentrations.

Clinical event-free survival was estimated with life table methods. Patients undergoing repeat cardiac surgery were censored at the time of the second operation. The log rank test for trend was used to compare survival probabilities between patients stratified by Lp(a) concentration tertiles. Hazard ratios were calculated for each tertile with the first tertile as base and are referred to as the relative risk with the appropriate 95% confidence intervals (CI). Deaths within 30 days of surgery were treated as censored in the analysis of late cardiac death and major events. To avoid the interdependence of multiple vein grafts in one patient and of multiple distal anastomoses in sequential grafts, vein graft occlusion was analysed by patient: that is, patients with at least one distal anastomosis occluded were compared with those with all distal anastomoses patent. The χ^2 test for trend was used to compare patients with and without angina, and patients with and without an occluded vein graft respectively. Relative risks with 95% CI were calculated for each tertile with the first tertile as base.

Results

PATIENT CHARACTERISTICS BEFORE OPERATION AND OPERATION DETAILS

The clinical and angiographic characteristics of the 353 patients studied are summarised in tables 1 and 2. Mean age (SD) at the time of surgery was 57·2 (7·3) years. Hypertension was present in 38% (defined if the patient was previously diagnosed as hypertensive, whether treated or not, and in any patients in whom the systolic blood pressure was more than 160 mm Hg or diastolic blood pressure more than 90 mm Hg, measured after a 10 minute rest). More than 60% had a history of preoperative myocardial infarction and 5% a history of heart failure; 98% reported recent angina, 73% with severe (grade III or IV) symptoms.

More than one quarter had three vessel disease and 13% had left main stem disease. Left ventricular function, assessed in the 30° right anterior oblique projection, was normal in 41% of patients; 29% of patients had only hypokinetic segments, while in a further 29% akinetic or dyskinetic segments were also present. A left internal mammary artery conduit was used in 75% of patients, and in only 6% of patients were internal mammary artery grafts the only conduits used.

Table 1 Clinical characteristics before coronary artery bypass graft surgery

Male	297	(84%)
Mean (SD) age, years	57·2	(7·3)
Non-white	3	(< 1%)
Angina	337	(98%)
Hypertension	133	(38%)
Diabetes	22	(6%)
History of hypercholesterolaemia	121	(35%)
Obesity (BMI > 25 kg/m²)	214	(61%)
Never smoked	57	(16%)
Former cigarette smoker	278	(80%)
Smoker at operation	11	(3%)
History of stroke/TIA	18	(5%)
History of claudication	58	(17%)
Previous myocardial infarction	215	(61%)
History of heart failure	19	(5%)
Renal disease (dialysis or transplant)	4	(1%)

BMI, body mass index; TIA, transient ischaemic attack.

Table 2 Severity of coronary artery disease and operation details*

Single vessel disease	68	(20%)
Two vessel disease	138	(40%)
Three vessel disease	94	(27%)
Left main stem disease	45	(13%)
Normal LV	141	(41%)
Only hypokinetic LV segments	101	(29%)
Akinetic or dyskinetic LV segment	101	(29%)
Mean (SD) number of graft conduits	2·74	(0·77)
Mean (SD) number of distal anastomoses	3·6	(1·20)
Patients with vein graft	332	(94%)
Patients with LIMA	266	(75%)
Patients with RIMA	46	(13%)
Patients with graft to LAD	311	(88%)
Patients with graft to diagonal	220	(62%)
Patients with graft to circumflex	269	(76%)
Patients with graft to intermediate	16	(5%)
Patients with graft to right coronary artery	281	(80%)

*Significant coronary artery disease is defined as reduction in artery lumen diameter of 75% or more in an epicardial coronary artery or a major branch supplying at least 25% of either the left anterior descending and diagonal territory, the circumflex territory, or the inferior territory. Stenosis of the left main stem is defined as a reduction in artery lumen diameter of 50%.
LV, left ventricle; LIMA, left internal mammary artery; RIMA, right internal mammary artery; LAD, left anterior descending coronary artery.

OUTCOMES

Mortality

Forty one patients died within five years of surgery and three had further cardiac surgery (two with repeat coronary artery bypass surgery nine and 51 months after initial surgery respectively, and one with cardiac transplantation 45 months after initial grafting). The actuarial survival of patients without further cardiac surgery 60 months after surgery was 87%. Fourteen patients (4·0%) died within 30 days of surgery. Twenty seven patients died between 30 days and 60 months after surgery. Sixteen of these deaths were cardiac deaths, of which 10 were sudden and five were due to an acute myocardial infarction. One death was unwitnessed in a patient who had a recent episode of unstable angina.

Non-fatal myocardial infarction

Overall, eight patients (2·3%) suffered at least one postoperative non-fatal myocardial infarction (excluding perioperative infarction), one of whom later died from a cardiac cause. Survival free from an admission with non-fatal infarction 60 months after surgery was 98%.

Angina

Two hundred and ninety one patients (94%) completed questionnaires at a mean (SD) of 59·1 (1·4) months after CABG surgery. One hundred and thirty nine patients (48%) suffered from angina. Of those with angina, 30 (22%) had grade 1, 60 (44%) grade 2, 35 (26%) grade 3, and 12 (9%) grade 4 symptoms.

Vein graft occlusion

Coronary and graft angiography was performed in 122 patients as part of the research protocol and in six patients for clinical indications at a mean (SD) of 60·2 (2·3) months after CABG surgery. Four angiograms could not be analysed for technical reasons. Five of the remaining patients had only internal mam-

Table 3 The association between Lp(a) lipoprotein concentration and outcome five years after coronary artery bypass graft surgery

	Tertile		
	1 (n = 116)	*2 (n = 115)*	*3 (n = 116)*
Lp(a) lipoprotein (mg/l)	0 to < 123	123 to < 331	331 to 1411
Whole cohort			
*Late cardiac death (beyond 30 days)	5	8	2
*Late cardiac death + MI	7	10	5
Angina	42/95 (44%)	44/93 (47%)	53/99 (53%)
Vein graft occlusion	16/38 (42%)	15/40 (38%)	20/40 (50%)
Upper tertile LDL (> 4·1 mmol/l, n = 115)			
Late cardiac death (beyond 30 days)	1/25	3/38	1/52
Late cardiac death + MI	1/25	4/38	3/52
Angina	10/18 (56%)	11/29 (38%)	25/47 (53%)
Vein graft occlusion	7/10 (70%)	3/10 (30%)	11/22 (50%)
Age < 55 years (n = 124)			
Late cardiac death (beyond 30 days)	3/49	1/41	1/34
Late cardiac death + MI	4/49	2/41	2/34
Angina	20/39 (51%)	21/39 (54%)	18/30 (60%)
Vein graft occlusion	8/22 (36%)	7/18 (39%)	6/13 (46%)

*One patient who died had no Lp(a) assays performed.
LDL, low density lipoprotein; MI, myocardial infarction.

mary conduits and in one patient the patency of one vein graft was unclear, the others being patent. Hence 118 patients with at least one vein graft were analysed. Fifty one patients (43%) had at least one distal anastomosis occluded.

Relation between Lp(a) concentration and cardiac status

A mean weighted Lp(a) concentration was obtained in 347 patients. The study cohort was divided into tertiles using the weighted mean Lp(a) concentration. Lp(a) concentration did not differ significantly between patients experiencing a late major cardiac event and those who did not, between those with and without angina, or between patients with and without at least one vein graft distal anastomosis occluded (tables 3 and 4). We also compared the mean log Lp(a) concentration of patients in the different outcome groups, and no significant differences between patient groups were found (data not shown).

A possible association between Lp(a) concentration and outcome which was restricted to patients with high concentrations of LDL cholesterol or to younger patients only was considered. Reanalysis of patients falling either into the highest LDL cholesterol tertile only (LDL cholesterol > 4·1 mmol/l) or patients aged less than 55 years did not show any significant relation between Lp(a) concentration and postoperative late major cardiac events, the presence of angina, or of at least one occluded vein graft five years after surgery (table 3).

Discussion

We have found no association between serum Lp(a) concentration and outcome five years after CABG surgery. During the first five years after CABG surgery, thrombosis, intimal hyperplasia, and atherosclerosis may all contribute to graft occlusion and we hypothesised that a high Lp(a) concentration, with its potential role in both thrombosis and atherosclerosis, may predict vein graft occlusion. We also hypothesised that a high Lp(a) concentration may predict clinical outcome. Symptoms of recurrent ischaemia and reduced survival early after operation are associated with graft occlusion and narrowing, while later both changes in grafts and progression of native disease are important.[10-12]

In patients with native coronary artery disease, serum Lp(a) concentration has been reported to be associated with the risk of myocardial infarction,[13-15] the presence of angiographically documented coronary disease,[1 16 17] and the progression of coronary disease without new myocardial infarction.[18] Apolipoprotein (a) has also been found in vein graft tissue resected from symptomatic patients undergoing repeat coronary artery bypass graft surgery.[19] Our results show that there may be no true association between Lp(a) concentration and graft occlusion or cardiac events within five years of CABG. The rate of graft occlusion is greatest during the first year and thereafter, during the next four years, occlusion occurs less frequently.[20] Technical factors[21] and recipient artery size[22] have an impact on the early outcome of surgery and it may be that it is factors such as these that are of greater significance early after operation. Thus graft atherosclerosis and its causes may be more important later, when a larger proportion of grafts are occluded by this mechanism.

Eritsland *et al*[3] have also reported that high serum concentrations of Lp(a) did not predict graft occlusion one year after CABG surgery. Both our study and that by Eritsland[3] contrast with two other studies in which serum Lp(a) concentration did predict vein graft disease.[2 23] However, there are important differences between these two positive studies and ours. In both studies reporting an association between Lp(a) concentration and graft disease there was selection bias, because patients underwent cardiac angiography for postoperative symptoms. In addition, the time interval after surgery when angiography was performed was wide, with a mean of 7 (range 0·7 to 14·3) years[2] and 95 (range 17 to 203) months[23] after surgery. The outcome was either a continuous measure of vein graft stenosis[2] or a combination of significant graft narrowing and occlusion.[23] Our study is distinct in being a prospective cohort study

Table 4 Relative risk (95% confidence interval) of an event in the second or third tertile Lp(a) lipoprotein concentration with the first tertile as base

	First tertile	*Second tertile*	*Third tertile*
*Late cardiac death (beyond 30 days)	1·00	1·63 (0·53 to 4·99)	0·40 (0·08 to 2·06)
*Late cardiac death + MI	1·00	1·46 (0·60 to 3·86)	0·72 (0·23 to 2·26)
Angina	1·00	1·07 (0·64 to 1·78)	1·21 (0·74 to 1·98)
Vein graft occlusion	1·00	0·89 (0·39 to 2·03)	1·19 (0·54 to 2·60)

*One patient who died had no Lp(a) assays performed.
MI, myocardial infarction.

examining both clinical and angiographic outcomes five years after CABG surgery and assessing graft disease by graft occlusion or patency.

The association between serum Lp(a) concentration and native coronary artery disease[24] and between Lp(a) concentration and vein graft stenosis[2] is reported to be greatest in younger patients or in those with raised LDL cholesterol.[25 26] In contrast, we have not found that stratification of our cohort by age or LDL cholesterol uncovered a significant association between coronary events and Lp(a) concentration.

LIMITATIONS OF THE STUDY

A weak association between Lp(a) concentration and outcome five years after CABG surgery may have remained undetected in our study. For late major cardiac events the smallest significant detectable difference between the upper and lower tertiles of Lp(a) concentration represents a relative risk of 2·3.

Lp(a) is an acute phase reactant, but we do not have C reactive protein concentrations available to evaluate this. However, our patients did not have unstable symptoms at the time of assessment before surgery, and sampling at intervals after surgery was avoided at times when an acute phase reaction was likely. We did not rely on one single assay, but used a weighted mean from a number of samples. In addition, an acute phase response as a result of graft closure would have strengthened any association, not weakened it.

Lp(a) concentration is mainly genetically determined. HMG co-reductase inhibitors reduce the synthesis of cholesterol and increase the catabolism of LDL by the LDL receptor pathway. Reports of the effects of these drugs on serum Lp(a) concentration are conflicting and they may increase[27] or have no effect on[28] Lp(a) concentrations. Five years after surgery only 36 patients were taking lipid lowering drugs and of these 11 were taking a statin. No patients who died were known to have taken a statin. With a lack of definitive data showing an impact of treatment with statins on Lp(a) concentration and only small numbers of patients treated any contribution of such therapy changes has been ignored.

CONCLUSION

The potential role of Lp(a) in both thrombosis and atherosclerosis raised the possibility that there may be an association between Lp(a) concentration and outcome after CABG surgery. In our consecutive group of 353 patients, serum Lp(a) concentration was not associated with outcome five years after CABG surgery.

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